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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DE (utility model), DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

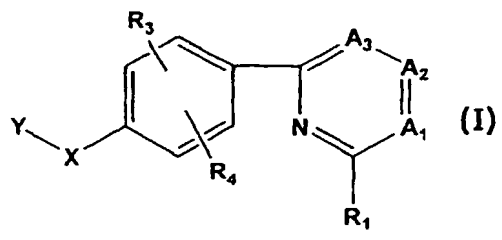
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
14 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYL SUBSTITUTED PYRIDINES, PYRIMIDINES, PYRAZINES AND TRIAZINES AND THE USE THEREOF



(I)

(57) Abstract: This invention relates aryl substituted pyridines, pyrimides, pyrazines and triazines of Formula (I): or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein A_1, A_2, A_3, R_1-R_4, X and Y are set in the specification. The invention is also directed to the use of compounds of Formula I for the treatment of neuronal damage following global and focal ischemia, for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), and for the treatment, prevention or amelioration of both acute or chronic pain, as antitinnitus agents, as anticonvulsants, and as antimanic depressants, as local anesthetics, as antiarrhytmics and for the treatment of prevention of diabetic neuropathy.

WO 01/68612 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/07797

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/81 C07D239/28 C07D239/38 C07D251/24 C07D241/24
C07D403/04 A61K31/505 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 095 240 A (FUJISAWA PHARMA.) 29 September 1982 (1982-09-29) the whole document ---	1,2,17, 50
X	CHEMICAL ABSTRACTS, vol. 96, no. 21, 1982 Columbus, Ohio, US; abstract no. 181290v, page 715; column 1; XP002178453 abstract & JP 81 104883 A (TANABE SEIYAKU) 20 August 1981 (1981-08-20) --- -/--	1,2,17, 50

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2001	09/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	YASUSHI HONMA ET AL.: "ANTIALLERGIC AGENTS.2.N-(1H-TETRAZOL-5-YL)6-PHENYL-2-PY RIDINECARBOXAMIDES." JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, 1983, pages 1499-1504, XP002178452 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 1499 -page 1503 ---	1,2,17
X	EP 0 507 962 A (KUMIAI) 14 October 1992 (1992-10-14) claims; examples 9,13; table 2 -----	1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2095240 A	29-09-1982	JP 1661221 C	19-05-1992
		JP 3028433 B	19-04-1991
		JP 57158779 A	30-09-1982
JP 81104883 A		NONE	
EP 507962 A	14-10-1992	AU 640283 B2	19-08-1993
		AU 8747391 A	26-05-1992
		CA 2066641 A1	26-04-1992
		DE 69132635 D1	19-07-2001
		DE 69132635 T2	20-09-2001
		EP 0507962 A1	14-10-1992
		WO 9207846 A1	14-05-1992
		JP 2779720 B2	23-07-1998
		JP 6316574 A	15-11-1994
		US 5403816 A	04-04-1995
		US 5391537 A	21-02-1995

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	George A. Doherty, et al.		
Serial No.:	10/571,334	Case 21268P	Art Unit: 1626
Filed:	March 7, 2006		
For:	3,5-ARYL, HETEROARYL or CYCLOALKYL SUBSTITUTED-1,2,4-OXADIAZOLES AS S1P RECEPTOR AGONISTS		Examiner: Nolan, Jason M

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Amendment is in response to the Office Action dated October 17, 2007, setting forth a shortened statutory period for response ending January 17, 2008. Please amend the above-identified application as set forth below.

Amendments to the Claims are reflected in the Listing of Claims which begins on page 2 of this paper.

Remarks begin on page 11 of this paper.

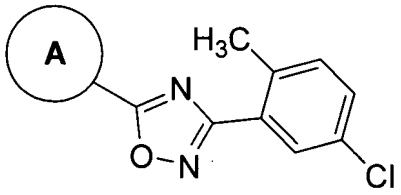
Amendments to the Claims:

This listing of claims replaces all prior versions, and listings, of claims in the application:

Listing of Claims:

1 to 8. (canceled)

9. (currently amended) ~~The~~ A compound ~~according to Claim 1~~ of formula Ia



Ia

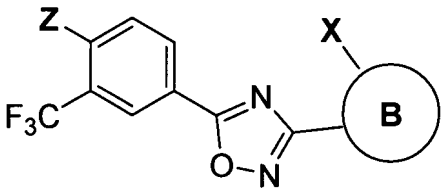
or a pharmaceutically acceptable salt thereof, wherein:

A is ~~selected from the group consisting of:~~ phenyl, ~~pyridyl and pyrazinyl,~~ substituted with one to two substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, halo-substitutedC_{1-6}alkyl, C_{3-6}cycloalkyl, halo-substitutedC_{3-6}cycloalkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy~~, or~~

~~A is C_{3-6}cycloalkyl, optionally substituted with one to two substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, halo-substitutedC_{1-6}alkyl, C_{3-6}cycloalkyl, halo-substitutedC_{3-6}cycloalkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy~~.

10. (canceled)

11. (currently amended) ~~The~~ A compound ~~according to Claim 1~~ of Formula Ic



Ic

or a ~~pharmacerutically~~ pharmaceutically acceptable salt thereof, wherein:

Z is selected from the group consisting of: C_{1-6}alkyl, halo-substitutedC_{1-6}alkyl, C_{3-6}cycloalkyl, halo-substitutedC_{3-6}cycloalkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

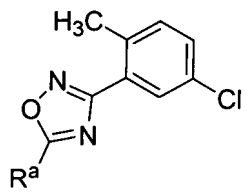
B is ~~selected from the group consisting of:~~ phenyl, ~~isoxazolyl, thiadiazolyl and thienyl, each~~ optionally substituted with a substituent selected from the group consisting of: halo, C_{1-4}alkyl, halo-substitutedC_{1-4}alkyl and hydroxy-substituted C_{1-4}alkyl; and

X is selected from the group consisting of: methyl, methoxy, nitro, amino, trifluoromethyl and halo, wherein **X** is substituted on the ring **B** ortho relative to the attachment of the 1,2,4-oxadiazole group shown in Formula [[I]] Ic.

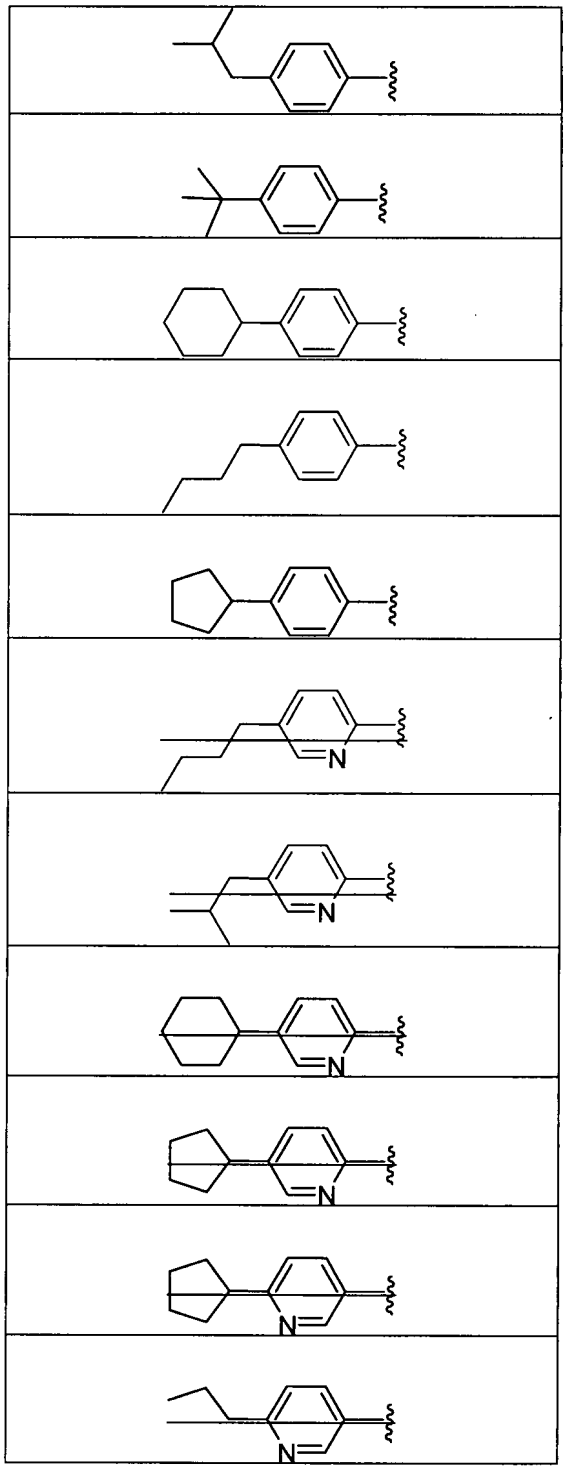
12. (original) The compound according to Claim 11 wherein **Z** is C_{1-6}alkoxy or halo-substituted-C_{1-6}alkoxy.

13. (currently amended) A compound selected from ~~one of~~ the following ~~tables~~ table:

TABLE A



Ra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N
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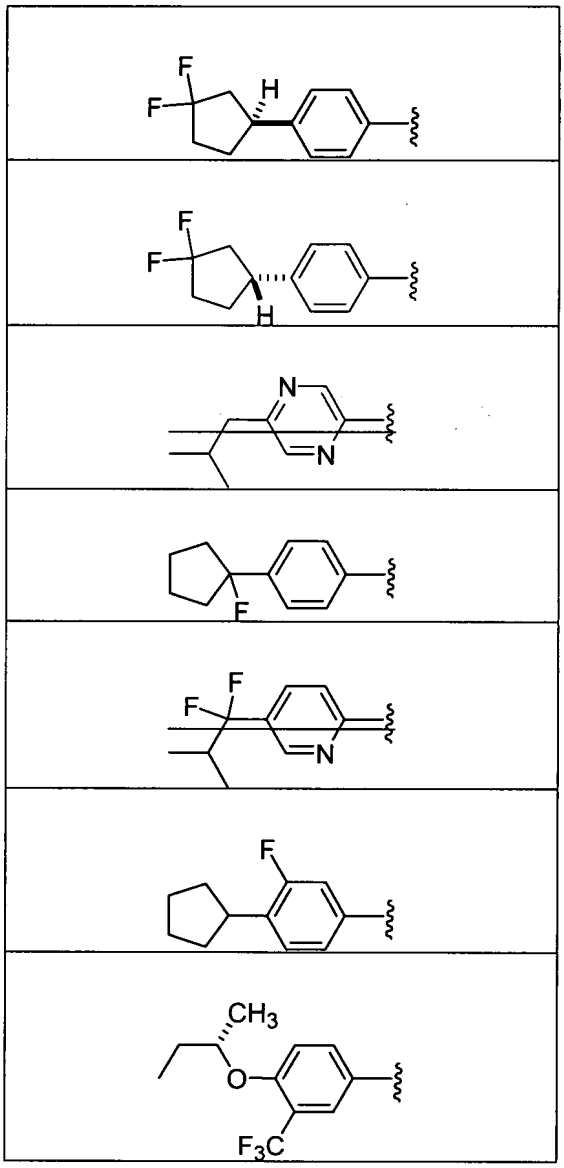

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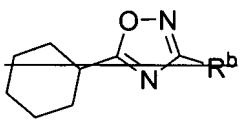
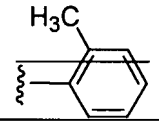
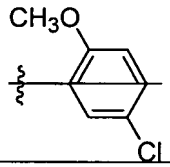
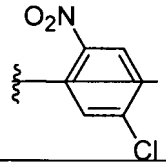
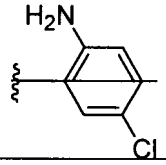
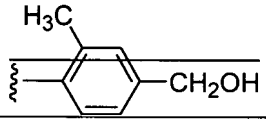
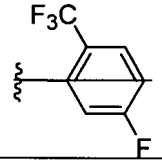
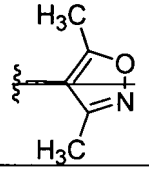
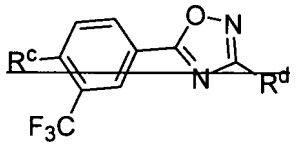
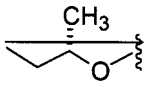
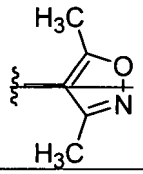
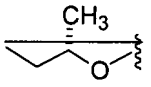
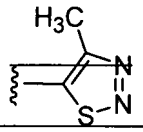
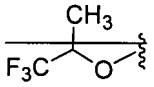
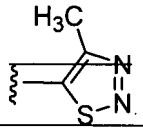
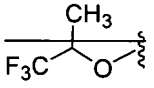
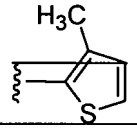
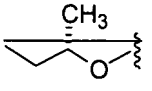
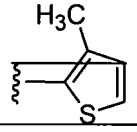
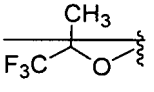
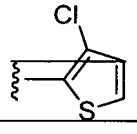


~~Rb~~








~~TABLE C~~



~~R^c~~	~~R^d~~
	
	
	
	
	
	

or a pharmaceutically acceptable salt of any of the above.

14. (currently amended) A method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with Claim [[1]] 9 in an amount that is effective for treating said immunoregulatory abnormality.

15. (original) The method according to Claim 14 wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: systemic lupus erythematosis, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

16. (original) The method according to Claim 14 wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

17. (original) The method according to Claim 14 wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma

and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

18. (original) The method according to Claim 14 wherein the immunoregulatory abnormality is selected from the group consisting of:

1) multiple sclerosis,
2) rheumatoid arthritis,
3) systemic lupus erythematosus,
4) psoriasis,
5) rejection of transplanted organ or tissue,
6) inflammatory bowel disease,
7) a malignancy of lymphoid origin,
8) acute and chronic lymphocytic leukemias and lymphomas and
9) insulin and non-insulin dependent diabetes.

19. (currently amended) A method of suppressing the immune system in a mammalian patient in need of immunosuppression comprising administering to said patient an immunosuppressing effective amount of a compound of Claim [[1]] 9.

20. (currently amended) A pharmaceutical composition comprised of a compound in accordance with Claim [[1]] 9 in combination with a pharmaceutically acceptable carrier.

21. (currently amended) A method of treating a respiratory disease or condition in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with Claim [[1]] 9 in an amount that is effective for treating said respiratory disease or condition.

22. (original) The method according to Claim 21 wherein the respiratory disease or condition is selected from the group consisting of: asthma, chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, infant respiratory distress syndrome, cough, eosinophilic granuloma, respiratory syncytial virus bronchiolitis, bronchiectasis, idiopathic pulmonary fibrosis, acute lung injury and bronchiolitis obliterans organizing pneumonia.

REMARKS

Reconsideration and allowance of the above-captioned patent application are respectfully requested. This application relates to 3,5-aryl, heteroaryl or cycloalkyl substituted-1,2,4-oxadiazoles as S1P receptor agonists.

Claims 1 to 22 are currently pending in the application. Claims 1 to 3 and 6 stand rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,994,478. Claims 1, 2 and 6 stand rejected under 35 U.S.C. § 102(b) as anticipated by Yale et al., J. Heterocyclic Chem. 1978, 15(8), pp. 1378-8. Claims 1, 2 and 6 stand rejected under 35 U.S.C. § 102(b) as anticipated by Korbonits, Chemische Berichte 1984, 117(11), pp. 3183-93. Claims 1, 2 and 6 stand rejected under 35 U.S.C. § 102(b) as anticipated by Srivastava et al., J. Brazilian Chem. Soc. 1993, 4(2), pp. 84-7. Claims 1 to 3, 6 and 8 stand rejected under 35 U.S.C. § 102(b) as anticipated by Diaz-Ortiz et al., Heterocycles 1996, 43(5), pp. 1021-30. Claims 1 (in part), 2(in part), 4, 5, 7, 9 (in part), 10, 11 (in part), 13 (in part), 14 to 19, 21 & 22 stand objected to for containing non-elected subject matter. Claims 9, 11, 12 and 20 stand objected to as being dependent upon rejected base Claim 1, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claim. This indication of allowability is appreciatively acknowledged.

This Amendment cancels Claims 1 to 8 and 10 and amends Claims 9, 11, 13, 14 and 19 to 21. Upon entry of this Amendment, claims in the application will be Claims 9 and 11 to 22.

The anticipation rejections are rendered moot by the cancellation of Claims 1 to 3, 6 and 8.

With respect to the claim objections, Claims 4, 5, 7 and 10 have been canceled, rendering the objection pertaining to these claims moot. Claims 9 and 11 have been rewritten in independent form and amended to cover only Group I subject matter. Likewise, Claim 13 has been amended to cover only Group I subject matter. Claim 20 has been amended to depend from Claim 9. Applicants respectfully request the objections to Claims 9, 11, 12, 13 and 20 be withdrawn.

Claims 14, 19 and 21 have been amended to depend from Claim 9. As such, Claims 14 to 19, 21 and 22 directly or indirectly depend from an allowable base claim. Applicants respectfully request the rejoinder of method Claims 14 to 19, 21 and 22 pursuant to M.P.E.P. § 821.04(b) and the withdrawal of the objection to these claims as drawn to non-elected subject matter.

Applicants submit that the application is in condition for allowance and passage thereto is earnestly requested. Any additional fees required in connection with this Amendment may be taken from Merck Deposit Account No. 13-2755. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the case.

Respectfully submitted,

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